DAF activity

The starting protein defined by claim 1 can be DAF; it would therefore have DAF activity. One can add to this protein SCRs known to confer C3b and/or C4b binding activity. This is clearly defined by the application. Conversely, one can add SCRs 2-4 of DAF to the other proteins to confer DAF activity. The language of the claims has been amended in an attempt to further clarify this point.

Indefiniteness

Structurally similar amino acids has been defined as the specific amino acids recited at page 15, lines 21-22, in claims 8, 9, 10, 23, 24, and 25.

The Markush language in claims 1, 8, 9, 16, 23, and 24 has been amended as suggested by the Examiner to delete the "and"; no occurrences of "group" not in combination with "consisting" could be found other than in claim 1.

The term "complement regulating" has been deleted from claims 8, 9, 23, and 24.

The term "analog" has been inserted into claims 13, 16, 23, 24, and 28.

Claims 23 and 24 have been amended to recite an explicit method step.

Claim 32 has been amended to make sense.

Rejections under 35 U.S.C. §102

Claims 1, 3, 12, 15, 16, 18, 27, 30, 31, and 32 were rejected under 35 U.S.C. §102(b) as disclosed by Lowell, et al., J. Exp. Med. 170, 1931-1946 (1989). This rejection is respectfully traversed if applied to the claims as amended.

The independent claims have been amended to exclude chimeras of CR1 and CR2. The claims are therefore novel over Lowell, et al.

Lowell never looks at, nor predicts, that one can alter functional activity, only binding activity, by changing SCRs from one protein into another protein. Lowell therefore cannot make obvious the subject of the amended claims. One would not predict that changing domains within a protein could confer a discrete activity since these are extremely large and complex proteins, and one would predict steric hindrance and other factors to interfer with the transfer of activity.

Allowance of all pending claims 1, 3-5, 8-16, 18-20, 23-32, and 34, as amended, is earnestly solicited. A copy of all claims as amended upon entry of this amendment is enclosed in an Appendix for the convenience of the Examiner.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Date: July 28, 1997

Patricia Hilger

Appendix: Claims as pending after entry of amendment

1. (five times amended) An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and those complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b or C3b and C4b.

3. (amended) The analog of claim 1 wherein the protein is complement receptor one.

4. (amended) The analog of claim 1 wherein the protein is decay accelerating factor.

5. (amended) The analog of claim 1 wherein the protein is factor H.

8. (five times amended) An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, [and] factor H, and these [complement regulating] proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; and substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A).

9. (six times amended) An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, [and] factor H, and these [complement regulating] proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein

analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13 selected from the group consisting of:
79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T (amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37: S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof.

10. (four times amended) An analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No. 4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof.

11. The analog of claim 1 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement

receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

12. The analog of claim 1 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

13. (twice amended) The analog of claim 1 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

14. (amended) The analog of claim 1 wherein the region of the protein having biological activity consists of three short consensus regions and has two complement regulatory activities.

15. The analog of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a patient in need thereof.

16. (four times amended) A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, [and] factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, comprising

constructing a DNA sequence encoding a protein analog selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b, or C3b and C4b, and

expressing the DNA sequence in a suitable host for expression of the protein analog.

18. (amended) The method of claim 16 wherein the protein used to form the analog is complement receptor one.

19. The method of claim 16 wherein the protein is decay accelerating factor.

20. The method of claim 16 wherein the protein is factor H.

23. (five times amended) A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, [and]

factor H, and these [complement regulating] proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos. 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A),

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

24. (five times amended) A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, [and] factor H, and these [complement regulating] proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T (amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37: S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino

acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof,

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

25. (four times amended) A method for making an analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of
180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No. 4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof.

26. The method of claim 16 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

27. (twice amended) The method of claim 16 comprising expressing a DNA encoding a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein and factor H, including in phase a DNA encoding [inserting into the protein analog] at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, not including combinations consisting of complement receptor 1 and complement receptor 2.

28. (twice amended) The method of claim 16 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

29. The method of claim 16 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

30. (amended) The method of claim 16 further comprising <u>isolated the analog and</u> mixing with the <u>isolated</u> analog a pharmaceutically acceptable carrier for administration to a patient in need thereof.

31. (amended) A DNA sequence which encodes an analog of claim 1.

32. (twice amended) The DNA sequence of claim 31 inserted into an expression vector operably linked to control sequences compatible with a [compatible] host <u>cell,</u> which is capable, when transformed into the [host cell] <u>expression vector</u>, of expressing a DNA encoding the analog of claim 1.

34. (twice amended) A method for enhancing the C4b or C3b cofactor activity of a complement regulatory protein, wherein the protein has either C3b or C4b cofactor activity, comprising adding sequences to the protein conferring binding of the other ligand, either C4b or C3b, wherein the sequences are present in a protein selected from the group of naturally occurring complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H<u>, not including combinations consisting of complement receptor 1 and complement receptor 2</u>.